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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/132,799	08/13/1998	UWE SCHOENROCK	BEIERSDORF-5	1033

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EXAMINER
BORIN, MICHAEL L

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/132,799	Applicant(s) Schoenrock et al.
	Examiner Michael Borin	Art Unit 1631

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) X Responsive to communication(s) filed on *Jul 29, 2002* .

2a) X This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) X Claim(s) *6 and 11-26* is/are pending in the application.

4a) Of the above, claim(s) *13, 21, and 23-26* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) X Claim(s) *6, 11, 12, 14-20, and 22* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐	Notice of References Cited (PTO-892)	4. ☐	Interview Summary (PTO-413) Paper No.s
2) ☐	Notice of Draftsperson's Patent Drawing Review (PTO-948)	5. ☐	Notice of Informal Patent Application (PTO-152)
3) ☐	Information Disclosure Statement(s) (PTO-1449) Paper No.s	6. ☐	Other:

DETAILED ACTION

1. Response filed 07/29/02 is acknowledged. Claims 1,3-5,7-10 are canceled. Claims 14-26 are added. The inconsistency in the number of pending claims is noticed. Applicant requests entry of new claims 14-25, submits claims 14-26 and describes, on p. 8 of the response, claims pending ending at claim #24. As all submitted claims are entered, claims pending are 6, 11-26. As before, claims drawn to non-elected group drawn to method of use, now claims 13,23-26 remain withdrawn from consideration. In regard to election of species, during an early stage of prosecution (during a telephone conversation with Attorney S. Ryan on 04/10/99), applicant elected, without traverse, a single monomer oligopeptide species of example 4 (Ac-VVRP-NH_2 ; p. 37); the pending claims were examined on merits to the extent they read on the elected species and, broader, on monomer oligopeptide VVRP, its amide and/or N-acetyl derivative. Current claims reading on the elected species, are 6,11-20,22-26. Claim 21 is withdrawn from consideration as drawn to non-elected species.

2. Rejections not reiterated from previous Office actions are hereby withdrawn. The following rejections constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 U.S.C. § 103.

It is noted that applicant preferred to address all art rejection of record together, by the way of discussing individually each of primary and secondary references. Consequently, applicant's arguments are addressed together, following re-statement of rejections as applied to the new set of claims.

3. Claims 14,15 are rejected under 35 U.S.C. 103(a) as obvious over Kohmura et al (Agric. Biol. Chem., 54, 835-836, 1990) and Stein (US 5,346,887) in view of Goodman & Gilman's "The pharmacological basis of therapeutics" (ninth edition, p. 745) and further in view of Greene et al. (US 5,753,226).

The rejection is maintained for the reasons of record set forth for claims 1,3.

The instant claims, defined in claim 14, item (a), and claim 15, are drawn to water-in-oil preparations comprising peptide VVRP.

Kohmura

Kohmura et al. describe fragments of human κ casein, in particular peptide having sequence VVRP (i.e., a peptide of the instant invention), and derivatives thereof. See p. 835, Table 1, compound No. 6, and 7-11. The referenced peptides exhibit a strong inhibitory effect on angiotensin-converting enzyme (ACE), the latter being an important regulator of blood pressure (see, e.g., p.835, second column).

Kohmura does not teach administration of the referenced peptides in a form of pharmaceutical composition.

Stein (US 5,346,887)

'887 patent teaches topical compositions comprising ACE inhibitors. Said compositions are used for treatment of glaucoma.

It would have been *prima facie* obvious to one skilled in the art at the time the invention was made to be motivated to prepare a topical pharmaceutical composition comprising peptides of Kohmura as an active ingredient, because Kohmura teaches that these peptides inhibit ACE activity and as such they can be used in topical pharmaceutical compositions of Stein. Note that **Goodman & Gilman's "The pharmacological basis of therapeutics"** (ninth edition, p. 743-751; submitted by applicants) teaches that "there is no compelling reason to favor one ACE inhibitor over another, since all ACE inhibitors have ... similar therapeutic indications, adverse effect profiles and contraindications." See p. 745, first full paragraph.

In regard to particular physical form of the preparation, water-in-oil dispersion, selection of a particular physical form of preparation is within perview of one skilled in the art. For example, Greene et al. (US 5,753,226) describes peptide formulations for topical treatment of ocular and skin sites. See col. 14, bottom and claims 1,24. The reference teaches a wide variety of physical forms, most preferable of which

being water-in-oil emulsions. Thus, selection of such physical form for topical ocular administration would be obvious to an artisan.

In regard to intended use recited in the preamble of claim 1, arguments related to the intended use of the composition are of little relevance in determining the patentability of the composition. A mere statement of purpose or intended use in the preamble of a claim need not be considered in finding anticipation. Divertech Corp. V. Century Steps, Inc.,7USPQ2d 1315 (Fed. Cir. 1988); In re Stencel, 4 USPQ2d 1071 (Fed. Cir. 1987). The motivation in the prior art to combine references need not be identical to that of the applicant to establish obviousness. In re Kemps, 40 USPQ2d 1309 (Fed. Cir., 1996). Further, the discovery of a new use for a prior art composition based on previously unknown properties of the structure may be patentable if claimed as a method; in the instant case the claims are drawn to a composition.

4. Claims 14,15 are rejected under 35 U.S.C. 103(a) as obvious over Kohmura et al (Agric. Biol. Chem., 54, 835-836, 1990) and Goodman & Gilman's "The pharmacological basis of therapeutics" (ninth edition, p. 745) and further in view of Cho et al (US 5,665,700).

The rejection is maintained for the reasons of record set forth for claims 1,3.

The instant claims, defined in claim 14, item (a), and claim 15, are drawn to water-in-oil preparations comprising peptide VVRP.

Kohmura

Kohmura et al. describe fragments of human κ casein, in particular peptide having sequence VVRP (i.e., a peptide of the instant invention), and derivatives thereof. See p. 835, Table 1, compound No. 6, and 7-11. The referenced peptides exhibit a strong inhibitory effect on angiotensin-converting enzyme (ACE), the latter being an important regulator of blood pressure (see, e.g., p.835, second column). Kohmura does not teach administration of the referenced peptides in a form of pharmaceutical composition.

Goodman & Gilman's

Goodman & Gilman's "The pharmacological basis of therapeutics" (the reference is submitted by applicants) teaches that the most frequently used ways of administration of ACE inhibitors is oral or intravenous. See pages 745, 746. Also, the reference teaches that there is no compelling reason to favor one ACE inhibitor over another, since all ACE inhibitors have ... similar therapeutic indications, adverse effect profiles and contraindications." See p. 745, first full paragraph.

Cho et al (US 5,665,700)

'700 patent teaches that various polypeptides can be administered orally in the form of water-in-oil formulations. See claims 1-3,20.

It would be *prima facie* obvious to one skilled in the art to be motivated to prepare pharmaceutical compositions from peptides of Komura because they have a desirable pharmaceutical properties of ACE inhibitors. Selection of a particular physical form of delivery would be within a perview of a person skilled in art. For example, an artisan would be motivated to use water-in-oil formulation which has proven to be effective for oral administration of various types of polypeptides, as illustrated in US 5,665,700.

In regard to intended use recited in the preamble of claim 1, arguments related to the intended use of the composition are of little relevance in determining the patentability of the composition. A mere statement of purpose or intended use in the preamble of a claim need not be considered in finding anticipation Divertech Corp. V. Century Steps, Inc.,7USPQ2d 1315 (Fed. Cir. 1988); In re Stencel, 4 USPQ2d 1071 (Fed. Cir. 1987). The motivation in the prior art to combine references need not be identical to that of the applicant to establish obviousness. In re Kemps, 40 USPQ2d 1309 (Fed. Cir., 1996). Further, the discovery of a new use for a prior art composition based on previously unknown properties of the structure may be

patentable if claimed as a method; in the instant case the claims are drawn to a composition.

5. Claims 14-20,22 remain rejected under 35 U.S.C. 103(a) as obvious over Kohmura et al, supra., and further in view of Bundgaard (Design of Prodrugs, Chapter 1, 1985) and Sumner-Smith (US 5,646,120). The rejection is maintained for the following reasons of record.

The rejection is maintained for the reasons of record set forth for claims 1,3,4.

The instant claims, in part defined in claim 14 b)-d), are drawn to compositions comprising peptide comprising sequence VVRP peptide and having acetyl protective group at N-terminus and/or amido group at C-terminus.

The Kohmura reference is applied as above. It is well known in the peptide art to administer peptide in a form of their prodrugs which have protected N- and/or C-termini because such substitution allows to optimize their solubility and/or stability and make them more suitable for pharmaceutical applications. The most common prodrugs are those requiring a hydrolytic cleavage mediated by enzymatic catalysis. See Bundgaard, p. 1. Sumner-Smith is cited to illustrate use of acetyl group to protect NH_2 terminal group, and amido-group, to protect COOH terminal group in peptides prepared for *in vivo* administration. See col. 2, lines 45-52,col. 6, lines 42-50, 53-62.

Therefore, it would have been *prima facie* obvious to one skilled in the art at the time the invention was made to use peptides described by Kohmura in pharmaceutical compositions in a form of a prodrug analog having protected N- and/or C-termini with a reasonable expectation that such prodrugs will have at least similar effectiveness in inhibition of angiotensin-converting enzyme and regulation of related physiological processes.

6. Claims 14,6,11,12 are rejected under 35 U.S.C. 103(a) as obvious over Kohmura et al. taken in combination with Stein and Goodman & Gilman's and Bundgaard and Sumner-Smith.

The rejection is maintained for the reasons of record set forth for claims 1,6,11,12.

The instant claims are drawn to concentration range, 0.000001-10%, of compositions defined in claim 14.

The references are applied as discussed above and in view of the following.

In regard to particular concentration ranges of the active ingredient in composition, Kohmura teaches that IC_{50} concentration of the referenced peptides is in the range 8-80μM, which corresponds to about 0.0005 - 0.005% (as compared to 0.000001 - 10% claimed range). If there are any differences between Applicant's

claimed preparations and that of the prior art, the differences would appear to be minor in nature. The instant invention's preparations, which fall within the scope of the prior art compositions, would have been *prima facie* obvious from said prior art disclosure to a person of ordinary skill in the art at the time the invention was made because, in the absence of sufficient factual evidence or unexpected results to the contrary, Applicant's claims are directed to optimization of an "art recognized variable" which is well within the perview of one of ordinary skill in the art.

Response to arguments

On the onset, applicants have traversed the primary and the secondary references pointing to the differences between the claims and the disclosure in each reference. Applicant is respectfully reminded that the rejection is under 35 USC103 and that unobviousness cannot be established by attacking the references individually when the rejection is based on the combination of the references. It has been well established that the test for combining references is not what individual references themselves suggest but what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art. *In re McLaughlin,* 170 USPQ 209 (CCPA 1970).

Applicant argues that the Stein reference requires ACE inhibitor to be used in conjunction with renin inhibitors included in the composition to reduce side effects of ACE inhibitors. However, the claim language "comprising" is open for other ingredients in the composition. Further, applicant argues that Stein is directed to ophtalmic, not cosmetic or dermatological administration. As discussed before, arguments related to the intended use of the composition are of little relevance in determining the patentability of the composition. Further, applicant argues whether captopril or enalapril (proline derivatives) can be considered as equivalents to slightly longer tetrapeptide ACE inhibitors of Kohmura. As was cited previously, Goodman & Gilman's "The pharmacological basis of therapeutics" teaches that there is no compelling reason to favor one ACE inhibitor over another, since all ACE inhibitors have ... similar therapeutic indications, adverse effect profiles and contraindications. Applicant did not provide any reason distinguishing the ACE inhibitors of Kohmura from their functional equivalents. As for "occasional" side effects cited by applicant, any drug has certain "occasional" side effects, and while it may not be absolutely certain that an ACE inhibitor will be completely free of side effects, a *prima facie* case of obviousness does not require absolute predictability of success.

In regard to Greene reference applicant attempts to argue that the reference is limited to use of antibodies. Applicant attention is directed to col. 3, bottom, of the

reference showing that active ingredients can be peptide fragments as well, and, more specifically, to claim 31 showing that peptide fragment may be a short peptide.

In regard to Bundgaard and Sumner-Smith references, the references have been used to demonstrate general knowledge in the art on preparation of peptide prodrug derivatives well known to allow to optimize their solubility and/or stability and make them more suitable for pharmaceutical applications.

Conclusion.

7. No claims are allowed

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (703) 305-4506. Dr. Borin can normally be reached between the hours of 8:30 A.M. to 5:00 P.M. EST Monday to Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Michael Woodward, can be reached on (703) 308-4028. The fax telephone number for this group is (703) 305-3014. Any inquiry of a general nature or relating the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

October 3, 2002

MICHAEL BORIN, PH.D
PRIMARY EXAMINER

mlb